REMARKS

Claims 1-6, 8, 10-12, 14-18, 20, 22-24, 26-29, and 31-40 are currently pending in this application. Claim 36 has been amended. New Claims 38-40 have been added. The amendment and new claims are supported by the specification and claims as filed.

Claim Rejection - 35 U.S.C. §103(a) - WO '374 in view of US '352

Claims 1-5, 8, 10-12, 14-17, 20, 23, 24, 26-29, and 31-37 have been rejected under 35 U.S.C. § 103(a) over WO 96/10374 ("WO '374") in view of U.S. Patent No. 6,143,352, ("US '352"). Independent Claims 1, 12, and 37, from which the other pending claims depend, recite, *inter alia* "a protective shell surrounding the therapeutic agent that prevents premature polymerization of the adhesive by blocking direct contact between the therapeutic agent and the cyanoacrylate surrounding said therapeutic agent" (Claim 1); "a protective shell surrounding the therapeutic agent preventing premature polymerization of the adhesive by blocking direct contact between the therapeutic agent and the cyanoacrylate surrounding said therapeutic agent" (Claim 12); and "forming a protective shell around an antibiotic to prevent premature polymerization of a liquid adhesive by blocking direct contact between the antibiotic and a cyanoacrylate" (Claim 37).

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See, e.g.*, M.P.E.P. § 2143. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Applicants assert that there is there is no reasonable expectation of success in preparing a cyanoacrylate adhesive as recited in Claims 1, 12, and 37 using the methods of US '352 (or WO '374). This assertion is supported by the Declaration of Yong-Hua Zhu, attached hereto. Affidavits or declarations containing evidence of

criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. § 103. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983).

In the Declaration, Dr. Zhu explains why one of ordinary skill in the art would not have a reasonable expectation of success in preparing a cyanoacrylate adhesive as claimed using the methods of US '352. As stated by Dr. Zhu, one of ordinary skill in the art understands that the microencapsulation efficiency, reflective of the actual amount of therapeutic agent that is encapsulated compared to the theoretical amount of therapeutic agent that could be encapsulated, can vary, e.g., depending upon the microencapsulation technique, the relative proportions of the encapsulant and therapeutic agent, and the process conditions. In support of this statement, Dr. Zhu provides literature references demonstrating that microencapsulation efficiency can vary widely, and that a high microencapsulation efficiency cannot necessarily be achieved in all situations (See AAPS PharmSciTech 2003; 4 (3) Article 39 (http://www.pharmscitech.org); Jang-Hyuk Ahn, Young-Pil Kim, Yu-Mi Lee, Eun-Mi Seo, Ki-Woong Lee, Hak-Sung Kim "Optimization of microencapsulation of seed oil by response surface methodology" Food Chemistry xxx (2007) xxx–xxx; Indian J. Pharm. Sci., 2006, 68 (4): 461-464; Acta Pharm. 55 (2005) 57–67; J. Dairy Sci. 84:1576–1582).

Dr. Zhu further explains that whether or not a low microencapsulation efficiency is acceptable, or instead whether a high microencapsulation efficiency is needed, depends upon the purpose of microencapsulation and the nature of the material to be encapsulated. If the purpose of the microencapsulation is to merely provide for sustained release or delayed release of the therapeutic agent, then a low microencapsulation efficiency may be acceptable – although a fraction of the therapeutic agent is unencapsulated and immediately available, the fraction of the therapeutic agent that is encapsulated will be released over time according to the microcapsules' release profile. Similarly, if the purpose of microencapsulation is to prevent contact of the therapeutic agent with a substance that destroys or deactivates the therapeutic agent, then a low microencapsulation efficiency may also be acceptable – although the fraction of the therapeutic agent that is unencapsulated will be destroyed or deactivated, the fraction of the therapeutic agent that is encapsulated will be protected from the other substance and thus remain active. On the

other hand, if the purpose of microencapsulation is to prevent contact of the therapeutic agent with another substance, because the therapeutic agent has a detrimental effect on the other substance, then a high microencapsulation efficiency may be necessary – the fraction of the therapeutic agent that is not encapsulated will cause the harm that is sought to be prevented, despite the fact that the remaining fraction of the therapeutic agent is encapsulated.

In Dr. Zhu's previous declaration dated April 6, 2005, he states that the majority of antibiotics contain active groups which react with cyanoacrylate adhesives. Accordingly, when an antibiotic is directly added to a cyanoacrylate, the antibiotic reacts with the cyanoacrylate such that polymerization occurs and the adhesive immediately solidifies, completely losing its adhesive function. Moreover, the antibiotic that reacts with cyanoacrylate becomes deactivated or exhibits a significant degradation in antibiotic activity. In Applicants' adhesives and methods, not only is the antibiotic sensitive to deactivation by the cyanoacrylate adhesive, the cyanoacrylate adhesive is sensitive to premature polymerization by the antibiotic. Dr. Zhu states that any unencapsulated antibiotic can potentially cause premature polymerization; hence, a high microencapsulation efficiency is needed.

As discussed in the Zhu Declaration, if controlled release of the antibiotic was the sole purpose for microencapsulation, then perhaps it could be argued that there would be some reasonable expectation of success in applying the methods of US '352 in microencapsulating antibiotics, as a low microencapsulation efficiency might be tolerated provided that at least some antibiotic was encapsulated. However, there can be no reasonable expectation of success if a high microencapsulation efficiency is needed. US '352 includes no teaching as to microencapsulation efficiency of the disclosed method and materials, much less specific information as to how to provide a high microencapsulation efficiency for an antibiotic instead of the disclosed pH modifiers, or using a gelatin encapsulant rather than the polymers of the examples. Because microencapsulation efficiency varies so widely dependent upon the encapsulant, the material to be encapsulated, the process conditions, and the microencapsulation technique, there can be no reasonable expectation of success in applying the methods of US '352 (or WO '374) to prepare microcapsules with a protective shell around an antibiotic to prevent premature polymerization of the cyanoacrylate by blocking direct contact between the antibiotic and the cyanoacrylate.

Accordingly, there is no reasonable expectation of success in preparing a cyanoacrylate adhesive as recited in Claims 1, 12, and 37 using the methods of US '352 (or WO '374), Applicants respectfully request the rejection of Claims 1-5, 8, 10-12, 14-17, 20, 23, 24, 26-29, and 31-37 be withdrawn.

Claim Rejection - 35 U.S.C. §103(a) - WO '374 in view of US '352 and WO '760

Claim 22 has been rejected under 35 U.S.C. § 103(a) over WO '374 in view of US '352, and further in view of WO 96/00760 ("WO '760"). Claim 22 depends from independent Claim 12 and specifies that in the method of Claim 12 "the wound comprises a skin laceration." Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Applicants assert that there is there is no reasonable expectation of success in preparing a cyanoacrylate adhesive as recited in the method of Claim 22 using the methods of US '352 or WO '760 (or WO '374).

WO '760 discloses an adhesive for sealing, e.g., surgically incised or traumatically lacerated tissues (WO '760, page 4, lines 11-12). However, WO '760 does not include any disclosure overcoming the deficiencies of WO '374 or US '352. WO '760 shares an inventor in common with US '352, and both claim priority to the same Application No. 08/266,674 filed June 28, 1994. Selected portions of the text as to the pH modifier are identical in both WO '760 and US '352, and the examples presented in both WO '760 and US '352 are identical. WO '760 includes no additional disclosure overcoming the deficiencies of US '352, namely WO '760 does not include any disclosure as to microencapsulation efficiency of the disclosed method and materials, much less specific information as to how to provide a high microencapsulation efficiency for an antibiotic instead of the disclosed pH modifiers, or using a gelatin encapsulant rather than the polymers of the examples.

For the same reasons as discussed above in regard to the rejection of Claim 12 over WO '374 and US '352, Applicants assert that the combination of WO '374, US '352, and WO '760 is insufficient to establish *prima facie* obviousness of Claim 22, in that there is no reasonable expectation of success in applying the methods of US '352 or WO '760 (or WO '374) to prepare microcapsules with a protective shell around an antibiotic to prevent premature polymerization of the cyanoacrylate by blocking direct contact between the antibiotic and the cyanoacrylate.

Applicants therefore respectfully request withdrawal of the rejection of Claim 22.

Claim Rejection - 35 U.S.C. §103(a) - WO '374 in view of US '352 and WO '685

Claims 6 and 18 have been rejected under 35 U.S.C. § 103(a) over WO '374 in view of US '352, and further in view of WO 99/20685 ("WO '685"). Claim 6 depends from independent Claim 1 and Claim 18 depends from independent Claim 12. Claims 6 and 18 claims specify that the polyethylene glycol employed as a defect forming agent has an average molecular weight of about 600. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Applicants assert that there is there is no reasonable expectation of success in preparing a cyanoacrylate adhesive as recited in Claims 6 and 18 using the methods of US '352 or WO '685 or WO '374.

WO '685 discloses use of a pore forming agent comprising polyethylene glycol of a molecular weight of from about 540 to about 8,000 (WO '685, page 9, lines 26-28). However, WO '685 does not include any disclosure overcoming the deficiencies of US '352 or WO '374. WO '685 is directed to coatings for sustained-release drug implants. WO '685 includes no disclosure as to cyanoacrylate adhesives. One of the embodiments of the disclosed invention involves an implant with an antibiotic present within the solid formulation or on the outer surface of the porous coating film (see WO '685, page 12, lines 7-10). An antibiotic positioned on the outer surface of the porous coating film would initiate premature polymerization of a cyanoacrylate adhesive were it to come into contact with same. Although WO '760 discloses an coating process that may provide some protection for the coated implant material, there is no disclosure of forming a protective shell, nor is there a disclosure of how much of the implant remains uncoated after completion of the disclosed coating process, nor it is not known whether or not the disclosed coating process would results in a coated form that will prevent premature polymerization of a cyanoacrylate by an antibiotic within the coating should the implant come into contact with the coated implant.

For the same reasons as discussed above in regard to the rejection of Claims 1 and 12 over WO '374 and US '352, Applicants assert that there is no reasonable expectation of success in applying the methods of US '352 or WO '685 or WO '374 to prepare microcapsules with a

protective shell around an antibiotic to prevent premature polymerization of the cyanoacrylate by blocking direct contact between the antibiotic and the cyanoacrylate.

Applicants therefore respectfully request that Claims 6 and 18 be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 10/4/07

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